## REMARKS/ARGUMENTS

With this amendment, claims 1, 6, 14-16, 19, 28, and 29 are pending. Claims 2-5, 7-13, 17, 18, and 20-27 are cancelled. For convenience, the Examiner's rejections are addressed in the order presented in the June 3, 2004 Office Action.

### I. Rejection under 35 U.S.C. §112, first paragraph, enablement

*1. Introduction*

Claims 1-6, 14-16, 19, and 25-28 were rejected as allegedly claiming subject matter that is not enabled by the specification. The Office Action states that nucleic acids encoding polypeptide variants are not enabled, as the instant claims encompass in their breadth any ILKAP polypeptide that has at least 90 or 95% identity to an amino acid sequence of SEQ ID NO:2. Office Action, page 2, lines 38-41. The Examiner further states that the rejection is proper as the specification discloses only one polypeptide with anti-angiogenic activity.

As identified in the Patent Office and the Federal Circuit, whether undue experimentation is required by one skilled in the art to practice an invention is determined by considering factors such as the amount of guidance presented in the application, the state of the prior art, and the presence of working examples. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985); *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). As described in *Wands*, a "considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should precede." *Wands*, 8 USPQ2d at 1404 (quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982).

The claimed methods specify that the ILKAP polypeptide has at least 90% identity to a reference amino acid sequence. Methods for determining percent identity are disclosed in the specification and are also well known to those of skill in molecular biology. These elements therefore provide adequate guidance for routine identification of the polypeptides of the invention. In addition, claims specify that the compound is identified by examining its angiogenic or anti-angiogenic effect on a cell expressing ILKAP. Therefore,

modulation of the ILKAP polypeptide by the test compound is correlated by angiogenic or anti-angiogenic phenotype. The level of skill in the biotechnological arts is considered to be very high. Therefore, given the high degree of identity claimed in the present application (at least 90%) and the assays provided which allow one of skill in the art to test whether such a polypeptide retains the claimed anti-angiogenic activity, Applicants respectfully submit that undue experimentation is not required to practice the claimed invention.

The level of identity (not "homology") required by the claims is intended to encompass other naturally occurring variants and alleles of human ILKAP that retain the anti-angiogenic activity of SEQ ID NO:2, as well as closely related orthologs that can be used in the assays of the invention. In addition, this level of identity is intended to encompass variants engineered for ease of experimental manipulation--for example, variants that include amino acids that can be modified so that the polypeptide can be more easily purified. Thus, Applicants are not attempting to "predict" the function of related proteins, but to provide coverage for polypeptides with minor sequence variations.

To prove his assertion that undue experimentation is required by one of skill in the art to make a functional ILKAP polypeptide having at least 90% identity to SEQ ID NO:2, the Examiner cites three references. The first, Atwood *et al.*, is relied upon for the proposition that functional assignments cannot be made to polypeptides based on "some degree of similarity between sequences." Applicants respectfully note that the claims in the instant application do not refer to "some degree of similarity" but require a strict identity (at least 90%) between the claimed polypeptides and the reference sequence. Similarly, the Examiner cites Skolnick *et al.* as teaching that assigning functional activities based on "sequence homology" is inaccurate. The Examiner is reminded of the difference between the terms "homology," referring to evolutionarily related sequences, and "identity," which requires an exact match in amino acid sequence, not evolutionarily conserved substitutions. These cited references are taken out of contact by the Examiner, as they teach that functional activity cannot be easily assigned to a polypeptide based only on "similarity" or "homology." This situation does not apply to the present application. The claims are not attempting to predict a function based on sequence similarity or homology. Rather, the claims encompass specific, minor variants of a reference

sequence, where the variants can be tested to ensure that they retain the claimed functional activity. Given the high level of skill in the biotechnology arts, one of skill could easily vary SEQ ID NO:2 by up to 90%, and then test to ensure that the polypeptide retains the claimed activity.

Moreover, the Examiner cites Metzler *et al.* as demonstrating that a single amino acid change can abolish the activity of a polypeptide, and concludes therefore that any variation of a polypeptide is unpredictable. However, this reference demonstrates quite the opposite conclusion--one of skill in the art can predict the effect of an amino acid change on the function of a polypeptide. In this particular reference, the goal of the study was to identify particular conserved residues as ligand binding sites. The authors demonstrated that the amino acid residues were important for binding by abolishing their function via mutation. Thus, the skilled practitioner in this example easily predicted the effect of altering an amino acid on the function of the protein.

Furthermore, some routine experimentation is tolerated by the enablement requirement. Again, given the high level of skill in the biotechnological arts, using the present invention the skilled practitioner would attempt to retain, not abolish, the activity of the polypeptide by suitable changes in the sequences--for example, the skilled practitioner would avoid inserting a run of 10 prolines in the sequence, which are known to alter the secondary structure of a polypeptide by creating bends or kinks. As described in the specification on page 10, line 28 to page 11, line 8, conservative amino acid substitutions are well known, where one amino acid is substituted by a chemically similar amino acid. The specification also lists a table of conservative amino acid substitutions. In the present application, for example, the skilled practitioner would likely avoid making significant changes to the PP2C-like phosphatase domain, which conferred anti-angiogenic activity to a partial ILKAP clone (see Example 1). If the change wrought by the skilled practitioner did indeed abolish the activity of the polypeptide, this result would be known using routine experimentation for anti-angiogenic activity, and that particular non-functional sequence would be discarded as an inoperable embodiment that is outside the scope of the claim.

Finally, the Examiner has asserted that the large number of possible variants creates a lack of enablement. However, regarding the issue of enablement for nucleic acids and polypeptide sequences, where a large number of possible embodiments exist, the PTO has provided express guidelines for examination. As set forth in the MPEP § 2164.08, a rejection of such claims such as those in the present application for undue breadth is inappropriate where one of skill could readily determine any one of the claimed embodiments.

This standard is further explained in the "Training Materials for Examining Patent Applications with respect to 35 U.S.C. § 112, first paragraph – Enablement Chemical/Biotechnological Applications," section III.A.2.b.i(c). In the guidelines, the PTO specifically answers the question regarding scope of a nucleic acid composition claim left open by the Federal Circuit in *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995). The claims at issue in *Deuel* were directed to any DNA encoding a specific amino acid sequence. Thus, a great number of nucleic acids were within the scope of the claims. In fact, the number was so great that a listing of all possible DNAs encoding the protein was a practical impossibility.

In the guidelines, the PTO addressed this issue, explaining that "even though a listing of all possible DNAs which encode a given protein is a practical impossibility due to the enormous number of such nucleic acids, any particular sequence can be written by one of skill given the disclosure and the sequence can be ordered from a company which synthesizes DNA." In this manner, one of skill in the art can readily determine any one of the embodiments. The PTO concluded that scope rejections such as the one hypothesized in *Deuel* should not be advanced.

In the present application, one of skill in the art has only to identify polypeptides, using well-know sequence algorithms, that have at least 90% identity to a conserved reference sequence. Although many such nucleic acids are possible, one of skill can readily determine, one by one, any particular ILKAP polypeptide, without undue experimentation. Furthermore, one of skill can use the assays described in the application to test the anti-angiogenic activity of the protein and easily determine if it falls within the scope of the claims. Thus, in the present application the skilled artisan can readily, with only routine experimentation, make and test any particular claimed nucleic acid.

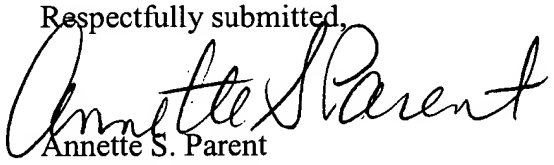
The assays described in the specification, coupled with methodology well known to those of skill in the art, therefore demonstrate that screening for compounds that modulate the angiogenic characteristics of an ILKAP polypeptide is routine. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Applicants therefore respectfully request that the rejection be withdrawn.

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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